(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68611 A1

(51) International Patent Classification[7]: C07D 237/04, 237/32, A61K 31/50, A61P 9/04

(21) International Application Number: PCT/FI01/00241

(22) International Filing Date: 12 March 2001 (12.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
20000577 13 March 2000 (13.03.2000) FI

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/68611 A1

(54) Title: PYRIDAZINYL PHENYL HYDRAZONES USEFUL AGAINST CONGESTIVE HEART FAILURE

(57) Abstract: Therapeutically active compounds of formula (I) in which R_1 to R_4 means hydrogen, alkyl, alkenyl, aryl, arylalkyl, carboxyalkyl, hydroxyalkyl or halogenalkyl, or R_2 and R_3 form a ring of 5-7 carbon atoms, R_5 to R_9 means hydrogen, alkyl, alkenyl, aryl, arylalkyl, acyl, hydroxy, alkoxy, alkoxycarbonyl, amino, acylamino, alkylamino, aryloxy, halogen, cyano, nitro, carboxy, alkylsulfonyl, sulfonamido or trifluoromethyl, wherein each aryl residue defined above by itself or as a part of another group may be substituted, and pharmaceutically acceptable salts and esters thereof. The compounds increase the calcium sensitivity of contractile proteins of the cardiac muscle and are thus useful in the treatment of congestive heart failure.

PYRIDAZINYL PHENYL HYDRAZONES USEFUL AGAINST CONGESTIVE HEART FAILURE

The present invention relates to pyridazinyl phenyl hydrazone compounds and pharmaceutically acceptable salts and esters thereof. The invention also relates to pharmaceutical compositions comprising such compounds as active ingredients. The compounds of the invention increase the calcium sensitivity of contractile proteins of the cardiac muscle and are thus useful in the treatment of congestive heart failure.

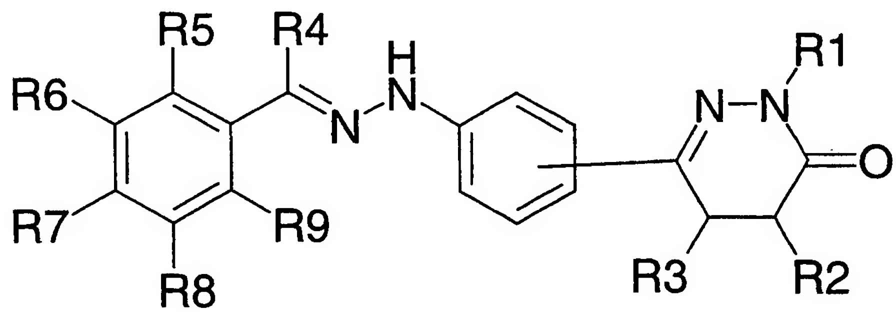
Congestive heart failure is characterized by a decrease in cardiac output and an increase in right and left ventricular filling pressure. These hemodynamic conditions can produce symptoms of dyspnea, fatigue and edema.

The contraction in cardiac muscle is triggered by the binding of calcium to contractile proteins. Series of phosphodiesterase isoenzyme III (PDE III) inhibitors are in clinical trials for the treatment of congestive heart failure. These compounds increase the contractility of the cardiac muscle and produce vasodilatation. However, it is known that the long-term application of those compounds may lead to calcium overload in the cardiac muscle and trigger arrhythmias. It is therefore desired to develop medicaments acting by a mechanism which would increase cardiac contractility without producing calcium overload. The increase of calcium sensitivity of contractile proteins would be such a mechanism.

Pyridazinyl phenyl hydrazone compounds have been described earlier in European patent application EP 383449. The compounds show calcium dependent binding to contractile proteins of the cardiac muscle, as well as PDE III inhibiting activity. In the specific examples one 1-acetyl-1-phenyl methylidene derivative is disclosed (Ex. 16). While the 1-acetyl-1-phenyl methylidene derivative has some effect in cardiac contractility, it does not increase the calcium sensitivity of contractile proteins.

Certain pyridazinyl phenyl hydrazone compounds appear as intermediates in European patent applications EP 223937 and EP 280224. However, the compounds are not specifically characterized. Mertens, A. et al., J. Med. Chem. 1990, 33, 2870-2875, discloses a phenyl, 4-methoxyphenyl and 2-hydroxyphenyl derivatives of pyridazinyl phenyl hydrazone compounds as intermediates.

It has now been found that compounds of formula (I) are potent in increasing the calcium sensitivity of contractile proteins in the cardiac muscle:



(I)

in which

R_1 to R_4 means hydrogen, alkyl, alkenyl, aryl, arylalkyl, carboxyalkyl, hydroxyalkyl or halogenalkyl, or R_2 and R_3 form a ring of 5-7 carbon atoms,

R_5 to R_9 means hydrogen, alkyl, alkenyl, aryl, arylalkyl, acyl, hydroxy, alkoxy, alkoxycarbonyl, amino, acylamino, alkylamino, aryloxy, halogen, cyano, nitro, carboxy, alkylsulfonyl, sulfonamido or trifluoromethyl,

wherein each aryl residue defined above by itself or as a part of another group may be substituted,

and pharmaceutically acceptable salts and esters thereof,

provided that a) when R_1, R_2, R_3, R_5, R_6, R_8 and R_9 are hydrogen and R_4 is methyl, R_7 is not hydrogen or methoxy and b) when R_1, R_2, R_3, R_5, R_6, R_7 and R_8 are hydrogen and R_4 is methyl, R_9 is not hydroxy.

The invention also relates to compounds of formula (I) in which R_1, R_2, R_3, R_5, R_6, R_8 and R_9 are hydrogen, R_4 is methyl, and R_7 is hydrogen or methoxy, or in which R_1, R_2, R_3, R_5, R_6, R_7 and R_8 are hydrogen, R_4 is methyl and R_9 is hydroxy and pharmaceutically acceptable salts and esters thereof, for use as a medicament.

In a class of preferred compounds and pharmaceutically acceptable salts and esters are compounds of formula (I) wherein R_5 to R_9 are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{6-10} aryl, C_{7-12} arylalkyl, C_{1-6} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, amino, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-10} aryloxy, halogen, cyano, nitro, carboxy, C_{1-6} alkylsulfonyl, sulfonamido or trifluoromethyl. In a subclass of this class of compounds and pharmaceutically acceptable salts thereof are compounds of formula (I) wherein R_5 to R_9 are independently hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, carboxy, C_{1-6} alkoxycarbonyl or nitro. In a subclass of this class of compounds and pharmaceutically acceptable salts thereof are compounds of

formula (I) wherein R_5 is hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, carboxy, C_{1-6} alkoxycarbonyl or nitro, most preferably hydroxy or nitro.

In another class of preferred compounds and pharmaceutically acceptable salts R_1 to R_4 are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{6-10} aryl, C_{7-12} arylalkyl, C_{1-6} carboxyalkyl, C_{1-6} hydroxyalkyl or C_{1-6} halogenalkyl, or R_2 and R_3 form a phenyl ring. In a subclass of this class of compounds and pharmaceutically acceptable salts thereof are compounds of formula (I) wherein R_1 to R_3 are independently hydrogen or C_{1-6} alkyl.

Each aryl residue in each of these preferred classes of compounds, by itself or as part of another group, may be substituted by 1 to 3, preferably 1 or 2, of fluorine, chlorine, bromine, iodine, hydroxy, nitro, carboxy, trifluoromethyl, amino, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-6} acyl, C_{1-6} carboxyalkyl, phenyl, naphthyl, halophenyl, halonaphthyl, benzyl, phenethyl, halobenzyl, halophenethyl, naphthylmethyl, naphthylethyl, C_{4-7} cycloalkyl, C_{1-4} alkyl C_{4-7} cycloalkyl, mono C_{1-4} alkylamino, di C_{1-4} alkylamino, C_{1-6} alkanoylamino, phenylcarbonylamino, naphthylcarbonylamino, cyano, thiol, or C_{1-6} alkylthio.

The compounds of formula (I) may contain one or more assymmetric centers and thus they can exist as enantiomers or diastereomers. The invention includes both mixtures and separate individual isomers.

Especially preferred individual compounds of the invention include:

(R)- 6-{4-[N'-(4-Hydroxy-3-methoxy-2-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one;

6-{4-[N'-(4-Hydroxy-3-methoxy-2-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one;

6-(4-{N'-[1-(2,5-Dihydroxy-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one;

6-(4-{*N*-[1-(2,4-Dihydroxy-3-methylphenyl)ethylidene]hydrazino}phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one;

6-(4-{N'-[Bis-(2,4-dihydroxy-phenyl)-methylene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one;

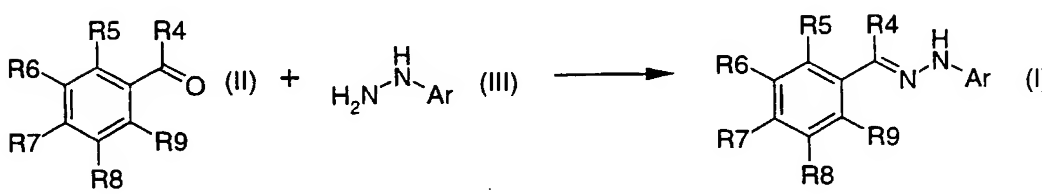
6-(4-{N'-[1-(2,4-Dihydroxy-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one;

2,6-Dihydroxy-3-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-benzoic acid ethyl ester; and

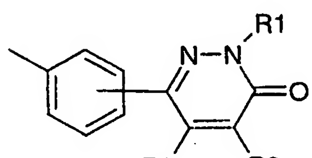
6-{4-[N'-(3-Ethyl-2,4-dihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one.

The compounds of the invention can be prepared by the well known condensation reaction between a carbonyl compound and a hydrazine as shown in Scheme 1:

Scheme 1. The hydrazones



wherein Ar means

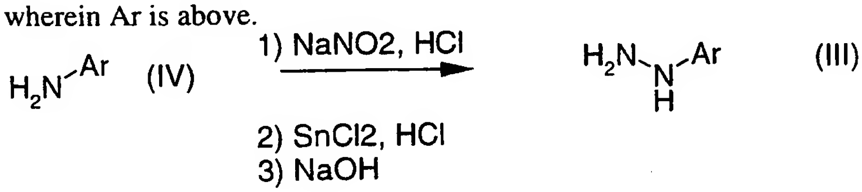


and R_1 to R_9 as defined above.

A suitable method for the preparation of hydrazines (III) is the diazotization of an aniline and reduction as a one pot synthesis. Scheme 2 shows this reaction:

Scheme 2. The hydrazines

wherein Ar is above.



where Ar is as above.

Compounds of formula (II) and (IV) are commercially available or can be prepared using methods known in the literature.

General method 1: In case where R_4 is hydrogen, the reaction of Scheme 1 is generally performed by refluxing a mixture of compounds (II) and (III) in a suitable solvent, such as ethanol, 2-propanol, acetonitrile or acetic acid, for 1-24 hours. The product (I) is filtered.

General method 2: In case where R_4 is not hydrogen, the reaction of Scheme 1 is generally performed by heating a neat mixture of compounds (II) and (III) at 140-170°C under inert atmosphere. The mixture is then triturated with ethyl acetate and the product (I) filtered.

Salts and esters of the compounds, when applicable, may be prepared by known methods. Physiologically acceptable salts are useful as active medicaments, however, preferred are the salts with alkali or alkaline earth metals. Physiologically acceptable esters are also useful as active medicaments. Examples are the esters with aliphatic or aromatic alcohols.

The term "alkyl" as employed herein by itself or as part of another group includes both straight, branched and cyclized chain radicals of up to 18 carbon atoms, preferably 1 to 8 carbon atoms, most preferably 1 to 4 carbon atoms. The term "lower alkyl" as employed herein by itself or as part of another group includes straight, branched and cyclized chain radicals of 1 to 7, preferably 1 to 4, most preferably 1 or 2 carbon atoms. Specific examples for the alkyl and lower alkyl residues, respectively, are methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, octyl, decyl and dodecyl including the various branched chain isomers thereof.

The term "acyl" as employed herein by itself or as part of another group refers to an alkylcarbonyl or alkenylcarbonyl group, the alkyl and alkenyl groups being defined above.

The term "aryl" as used herein by itself or as part of another group refers to a monocyclic or bicyclic group containing from 6 to 10 carbon atoms in the ring portion. Specific examples for aryl groups are phenyl, naphtyl and the like. "Aroyl" means in a corresponding way an arylcarbonyl group.

The term "alkoxy" as employed herein by itself or as part of another group includes an alkyl group as defined above linked to an oxygen atom. "Aryloxy" means in a corresponding way an aryl group linked to an oxygen atom.

The term "substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine or trifluoromethyl group, amino, alkyl, alkoxy, aryl, alkyl-aryl, halogen-aryl, cycloalkyl, alkylcycloalkyl, hydroxy, alkylamino, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, or alkylthio substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2 of the above mentioned substituents.

Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 0.1 to 500 mg per day depending on the age, weight, condition of the patient, administration route and the phospholamban inhibitor used. The compounds of the invention can be formulated into dosage forms using the principles known in the art. It can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The compositions containing the active compound can be given enterally or parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about 0.5 to 100 %, preferably from about 0.5 to about 20 %, per weight of the total composition.

The usefulness of the compounds of the invention is demonstrated by the following experiments.

Experiment 1. Calcium sensitizing effect in skinned cardiac fiber

Method

The heart of a guinea-pig was excised and perfused with ice-cold saponin (125 mg/l) skinning solution consisting of (mM): K^+-acetate 74.7, EGTA-Na_2 10, $MgSO_4$ 5.4, ATP-Na_2 4, MOPS 20, pH 7.0 (by 1 M KOH). Left ventricular papillary muscle was dissected and sonicated at 10 Watt for 60 s. The distance between ultrasound probe and the papillary muscle was 10 mm. The fibres (< 200 μm in diameter) were dissected from the surface of sonicated papillary muscles in the same solution.

The fibre was glued between platinum wires, one attached to an isometric force transducer (type AE-801, SensoNor, Horten, Norway) and another to a micro manipulator. The fibre was relaxed in a solution consisting of (mM): EGTA-Na_2 10, $MgSO_4$ 5.4, ATP-Na_2 4, MOPS 20. The pH of the solution was adjusted to 7.0 and ionic strength to 0.16 M by the addition of KOH and K^+-acetate. Creatine kinase and creatine phosphate were not added as an ATP generating system because the developed tension was well sustained for the time required for experiment. The calculations for ionic strength and for free calcium (pCa 7.0-6.2) were performed using a suitable program. The fibres were stretched in relaxing solution until resting tension was just noticeable. When the calcium (pCa 6.0 or 6.2)-induced tension had reached steady state the test compound (final concentrations 0.1, 0.3, 1, 3, and 10 μM) was cumulatively added into the solution at 6 min intervals. All the experiments were carried out with fresh fibres at normal room temperature.

Results

The calcium sensitizing effect of the compounds are shown in Table 1.

TABLE 1. Maximum calcium sensitizing effect in skinned fiber (change in force, % change from control). The Reference compound is Ex. 16 of EP 383449.

Compound of Example No.	Change in force / % change from control
2	207.2
6	32.9
21	44.2
23	39.9
24	42.0
33	55.2
34	52.8
35	25.4
37	21.7
38	32.2
40	100.2
43	39.0
49	28.7
Ref. compound	No effect

Experiment 2. Effect in left ventricular pressure derivatives in isolated heart

After sacrification the heart of a guinea-pig was rapidly excised and rinsed in oxygenated perfusion buffer. A cannula was inserted into the aorta and secured with a ligature. Retrograde perfusion began as soon as the heart was placed in a thermostatically controlled moist chamber of the Langendorff apparatus (Hugo Sachs Elektronik, KG). Modified Tyrode solution (37 °C), equilibrated in a thermostatically controlled bulb oxygenator with carbogen (95 % O_2 and 5% CO_2), was used as a perfusion buffer. The composition of the Tyrode solution was (in mM): NaCl 135; $MgCl_2$ x $6H_2O$ 1; KCl 5; $CaCl_2$ x $2H_2O$ 2; $NaHCO_3$ 15; Na_2HPO_4 x $2H_20$ 1; glucose 10; pH 7.3-7.4. The perfusion buffer was delivered at the top of the oxygenator by a pump and driven automatically by its controller. Subsequently, the buffer was delivered into the bulbs of the oxygenator chamber by a rotating disk. It was dispersed by making a thin fluid film on a large inner oxygenator surface in O_2/CO_2 atmosphere leading to saturation of the perfusate with oxygen (partial pressure 660 mmHg at 37 °C).

The experiments were carried out under constant pressure condition (50 mmHg). After a short prestabilization (10 min) a latex balloon (size 4) was carefully placed into the left ventricle through the left pulmonary vein and the left atrium. The latex balloon was attached to a stainless-steel cannula coupled with a pressure transducer. The latex balloon, the cannula and the chamber of the pressure transducer were carefully filled with ethylene glycol / water (1:1) mixture avoiding any air-bubble. The isovolumetric left ventricular pressure was recorded through the pressure transducer. At the beginning of the experiment, the volume of the balloon was adjusted to obtain a diastolic pressure of approximately 5 mmHg. Before starting the experiment the heart was allowed to stabilise further for 30 - 50 min. The systolic and end-diastolic left ventricular pressures were recorded for calculating the maximal positive and negative derivatives of the left ventricular pressure.

Results

The EC_{50} values (μM) of various compounds of the invention on maximal positive derivative of the left ventricular systolic pressure are shown in Table 2.

Compound of Example No.	EC_{50} (μM)
2	0.02
6	0.31
21	3.04
23	2.47
33	0.4
34	0.11
35	0.31
40	0.71
43	1.75
49	0.25

To further illustrate the invention, but not by way of limitation, the following examples are provided. The melting points were determined on a Reichert plate melting point apparatus and were not corrected. NMR-spectra were recorded on using a Bruker ARX 400 spectrometer with internal TMS as the reference (0 ppm).

EXAMPLES

Example 1 (intermediate compound).
(R)-6-(4-hydrazino-phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

A slight modification on the procedure described in J.Med.Chem. (1990), 33(10), 2870-2875 was used as follows. A solution of sodium nitrite (1.7 g) in water (12.5 ml) was added slowly at 0-5 °C to a solution of (R)-6-(4-aminophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (5 g) in 1 M hydrochloric acid (75 ml). The resulting solution was stirred on ice bath for five minutes and then added slowly to a solution of tin(II)chloride dihydrate (17 g) in 1 M hydrochloric acid (150 ml) keeping the reaction temperature below 5 °C. This solution was stirred on ice for forty minutes and then a solution of 50% NaOH (75 ml) was quickly added. The resulting mixture was stirred on ice bath until the temperature reached zero degrees Celsius. The crystals were filtered and washed with dilute ammonia. Yield: 5.0 g, 93 %.

HPLC: enantiomerically pure.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.04 (d, 3H, CH_3), 2.17 (d, 1H, J = 16 Hz), 2.60 (m, 1H), 3.29 (m, 1H), 4.04 (s, 2H, NH_2), 6.77 (d, 2H, J = 8 Hz), 7.09 (b, 1H, NH), 7.54 (d, 2H, J = 8 Hz), 10.66 (s, 1H, NHCO).

Example 2.
(R)- 6-{4-[N'-(4-Hydroxy-3-methoxy-2-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

A solution of 4-hydroxy-3-methoxy-2-nitro-benzaldehyde (1.6g) in ethanol (15 ml) was added to a suspension of (R)-6-(4-hydrazino-phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (1.75 g) in ethanol (20 ml) and the resulting mixture refluxed for two hours. The resulting crystals were filtered at room temperature and washed with ethanol. Yield 2.37 g. HPLC: purity 99.4 %, optical purity 99.8 %.

^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 3H, CH_3), 2.18-2.22 (m, 1H), 2.64 (m,1H), 3.34 (m, 1 H), 3.84 (s, 3H, CH_3O), 6.98 (d, 2H), 7.08 (d, 1H), 7.37 (d, 1H), 7.66 (d, 2H), 7.67 (s, 1H), 10.68 (s, 1H, NH), 10.77 (s, 1H, NHCO).

Further examples

The following compounds were synthesized according to the General method 1 (as exemplified in the previous example) or according to the General method 2.

General method 1:

Reflux a mixture of a hydrazine derivative (II) and a benzaldehyde derivative (III) in a suitable solvent (ethanol, 2-propanol, acetonitrile or acetic acid) for 1-24 hours. Filter the product.

General method 2:

Heat a neat mixture of a hydrazine derivative (II) and a ketone (III) at 140-170°C under inert atmosphere. Triturate with ethyl acetate and filter the product.

The following compounds are synthesized according to the general method 1 unless otherwise specified.

Example 3.

2,6-Dihydroxy-3-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-benzoic acid ethyl ester

Yield 73 %, Melting point: 203 –208 °C

^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.20-2.23 (m, 1H), 2.64-2.68 (m, 1H), 3.30-3.33 (m, 1H), 3.83 (s, 3H, $COOCH_3$), 6.49 (d, 1H), 6.93 (d, 2H), 7.40 (d, 1H), 7.69 (d, 2H), 8.09 (s, 1H), 10.40 (s, 1H), 10.57 (s, 1H), 10.76 (s, 1H). 11.54 (s 1H).

Example 4.

6-{4-[N'-(2,4,5-trihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 82 %, Melting point: 286-290 °C

^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.18-2.22 (m, 1H), 2.61-2.67 (m, 1H), 3.30-3.35 (m, 1H), 6.32 (s 1H), 6.93-6.95 (m, 1H), 7.66 (d, 2H), 8.03 (s, 1H), 8.42 (s, 1H), 9.24 (s, 1H), 9.76 (s, 1H), 10.32 (s, 1H), 10.74 (s, 1H).

Example 5.

6-{4-[N'-(2-Hydroxy-5-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 89 %, Melting point: 299-300°C
^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.19-2.23 (m, 1H), 2.63-2.68 (m, 1H), 3.31-3.37 (m, 1H), 7.05-7.10 (m ,3H), 7.72 (d, 2H), 8.05-8.08 (m ,1H), 8.21 (s, 1H), 8.55-8.56 (m , 1H), 10.78 (s, 1H), 10.89 (s, 1H), 11.61 (s, 1H).

Example 6.

6-{4-[N'-(4-Hydroxy-3-methoxy-2-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 87 %, Melting point: 235-239 °C
^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.18-2.22 (m, 1H), 2.62-2.68 (m, 1H), 3.31-3.34 (m ,1H), 3.84 (s, 3H, CH_3O), 6.98 (d, 2H), 7.08 (d, 1H), 7.37 (d, 1H), 7.65 (d, 2H), 7.67 (s, 1H), 10.67 (s, 1H), 10.76 (s, 1H).

Example 7.

6-{4-[N'-(2,3-Dihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 69 %, Melting point: 245-247 °C
^{1}H-NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.19-2.23 (m 1H), 2.64-2.68 (m, 1H), 3.33-3.38 (m, 1H), 6.68-6.77 (m, 2H), 6.99-7.03 (m, 3H), 7.70 (d, 2H), 8.17 (s, 1H), 9.2 (b, 1H), 9.95 (s, 1H), 10.63 (s, 1H), 10.77 (s, 1H).

Example 8.

6-{4-[N'-(2,5-Dihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 89 %, Melting point: 317-320 °C
^{1}H-NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.18-2.22 (m, 1H), 2.62-2.68 (m, 1H), 3.30-3.36 (m, 1H), 6.59-6.62 (m, 1H), 6.69-7.03 (m, 1H), 7.68 (d, 2H), 8.12 (s, 1H), 8.82 (s, 1H), 9.57 (s, 1H), 10.57 (s, 1H), 10.76 (s, 1H).

Example 9.

6-{4-[N'-(3,4-Dihydroxy-2-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 70 %, Melting point: 239-241 °C
^{1}H-NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.18-2.22 (m, 1H), 2.61-2.67 (m, 1H), 3.33-3.38 (m, 1H), 6.94-6.98 (m, 1H), 7.06 (d, 1H), 7.64-7.66 (m, 3H, ArH, CH=N),

9.94 (b, 1H), 10.48 (b, 1H), 10.59 (s, 1H), 10.75 (s, 1H).

Example 10.

2-{[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-benzoic acid

Yield: 61 %, Melting point: 250-251 °C

^{1}H-NMR (DMSO-d_6): δ = 1.12 (d, 3H), 2.25-2.30 (m, 1H), 2.72-2.78 (m, 1H), 3.42-3.51 (m, 1H), 7.72 (d, 2H), 7.90-7.95 (m, 3H), 7.98-8.05 (m, 2H), 8.34-8.36 (m 1H), 8.61 (s, 1H), 11.03 (s, 1H).

Example 11.

6-{4-[N'-(2-trifluoromethyl-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 62 %, Melting point: 113-115 °C

^{1}H-NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.19-2.23 (m, 1H), 2.63-2.69 (m, 1H), 3.33-3.37 (m, 1H), 7.14 (d, 2H), 7.50-7.52 (m,1H), 7.68-7.75 (m, 4H), 8.19-8.27 (m, 2H), 10.79 (s, 1H), 11.04 (s, 1H).

Example 12.

Acetic acid 2-methoxy-4-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-3-nitro-phenyl ester

Yield: 65 %, Melting point: 220-223 °C.

^{1}H-NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.18-2.23 (m, 1H), 2.38 (s, 3H, $OCOCH_3$), 2.62-2.67 (m, 1H), 3.33-3.38 (m, 1H), 3.85 (s, 3H), 7.03 (d, 2H), 7.46 (d, 1H), 7.60 (d, 1H), 7.72 (d, 2H), 7.75 (s, 1H), 10.79 (s, 1H), 10.98 (s, 1H).

Example 13.

6-(4-{N'-[1-(3,5-Dihydroxy-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

The title compound was prepared according to the general method 2.

Yield: 27 %, melting point 162-166 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.07 (d, 3H), 2.17 (s, 3 H), 2.18-2.22 (m, 1H), 2.62-2.68 (m, 1H), 3.35-3.41 (m, 1H), 6.17 (s, 1H), 6.67 (s, 2H), 7.23 (d, 2H), 7.67 (d, 2H), 9.21 (s, 1H), 9.44 (s, 1H), 10.75 (s, 1H).

Example 14.

6-(4-{N'-[1-(2,4-Dihydroxy-phenyl)-3-(3,4-dimethoxy-phenyl)-propylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

The title compound was prepared according to the general method 2
Yield: 71 %, melting point 135-140 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.07 (d, 3H), 2.19-2.23 (m 1H), 2.64-2.67 (m, 1H), 2.77 (t , 2H), 3.15 (t, 2H), 3.31-3.33 (m 1H), 3.69 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.29-6.35 (m, 2H), 6.83-6.87 (m 2H), 6.93 (d, 1H), 7.03 (d, 2H), 7.36 (d, 1H), 7.71 (d, 2H), 9.1 (s, 1H), 9.5 (s, 1H), 10.78 (s, 1H), 12.91 (s, 1H).

Example 15.

4-(4-{N'-[(2,4-Dihydroxy-phenyl)-phenyl-methylene]-hydrazino}-phenyl)-2*H*-phthalazin-1-one

The title compound was prepared according to the general method 2.
Yield: 95 %, melting point 160-170 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.7 (m,2 H), 7.3-7.9 (m,13 H), 8.3 (m,1 H), 10.1 (s,1H), 10.7 (s,1H), 12.1 (s,1H), 12.7(s,1H).

Example 16.

4-(4-{N'-[(2,4-Dihydroxy-phenyl)-(4-hydroxy-phenyl)-methylene]-hydrazino}-phenyl)-2*H*-phthalazin-1-one

The title compound was prepared according to the general method 2.
Yield: 95 %, melting point 150-160 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.3 (m,2H), 6.8 (m,2 H), 7.4-7.9 (m,10H), 8.3 (m,1H), 10.1 (s,1H), 10.2 (s,1H), 10.4 (s,1H), 12.1 (s,1H), 12.7 (s,1H)

Example 17.

4-(4-{N'-[Bis-(2,4-dihydroxy-phenyl)-methylene]-hydrazino}-phenyl)-2*H*-phthalazin-1-one

The title compound was prepared according to the general method 2.
Yield 60 %, melting point 140-146 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.3 (m,4H), 7.1-8.3 (m,10H), 10.1 (s,1H), 10.2 (s,2H), 11.2 (s,2H) 12.7(s,1H).

Example 18.

4-{4-[N'-(2,4-Dihydroxy-benzylidene)-hydrazino]-phenyl}-2*H*-phthalazin-1-one

Yield:50 %, melting point 278-283 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.3(m,1H),6.4(m,1H),7,.4-7,.9 (m,8H), 8.3(m,1H), 8.9(s,1H), 10.3 (s,1H),12.8 (s,1H),13.4 (s,1H).

Example 19.

6-{4-[*N'*-(4-Methanesulfonylbenzylidene)hydrazino]phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield: 54.3 %, mp 130-137 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.08 (d. 3H, CH_3), 2.21 (d, 1H, CH), 2.66 (d of d, 1H, CH), 3.22 (s, 3H, CH_3), 3.33 (m, 1H, CH), 7.17 (d, 2H, CH), 7.71 (d, 2H, CH), 7.97 (s, 1H, CH), 10.79 (s, 1H, NH), 10.95 (s, 1H, NH).

Example 20.

3-{[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]-hydrazonomethyl}-benzonitrile

Yield: 60 %, mp 220-224 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.08 (d, 3H, CH_3), 2.22 (d, 1H, CH), 2.66 (d of d, 1H, CH), 3.35 (m, 1H, CH), 7.16 (d, 2H, CH), 7.59 (t, 1H, CH), 7.69 (d, 2H, CH), 7.74 (d, 1H, CH), 7.92 (s, 1H, CH), 8.01 (d, 1H, CH), 8.10 (s, 1H, CH). 10.78 (s, 1H, NH), 10.86 (s, 1H, NH).

Example 21.

6-{4-[*N'*-(2,4-Dihydroxybenzylidene)hydrazino]phenyl}-5-methyl-2*H*-pyridazin-3-one

The product was recrystallized from dimethylformamide.
Yield: 55 %, mp 303-310°C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.16 (s, 3H, CH_3), 6.35 (m, 2H, CH), 6.79 (s, 1H, CH), 6.97 (d, 2H, CH), 7.34 (m, 3H, CH), 8.10 (s, 1H, CH), 9.69 (s, 1H, OH), 10.33 (s, 1H, NH), 10.63 (s, 1H, OH), 12.90 (s, 1H, NH).

Example 22.

6-{4-[*N'*-(4-Hydroxy-3-methoxy-2-nitrobenzylidene)hydrazino]phenyl}-5-methyl-2*H*-pyridazin-3-one

Yield: 71.0 %, mp 264-268 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.15 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.79 (s, 1H, CH), 7.01 (d, 2H, CH), 7.09 (d, 1H, CH), 7.33 (d, 2H, CH), 7.38 (d, 1H, CH), 7.68 (s, 1H, CH), 10.62 (s, 1H, NH), 10.65 (s, 1H, OH), 12.91 (s, 1H, NH).

Example 23.

6-{4-{*N'*-[1-(2,4-Dihydroxyphenyl)ethylidene]hydrazino}phenyl}-5-methyl-2*H*-pyridazin-3-one

The title compound was prepared according to the general method 2. The product was refluxed in propionitrile with acetic acid as a catalyst.
Yield: 32 %, mp 299-303 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.16 (d, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.28 (d, 1H, CH), 6.33 (d of d, 1H, CH), 6.79 (d, 1H, CH), 7.07 (d, 2H, CH), 7.38 (d, 1H, CH), 7.39 (d, 2H, CH), 9.50 (s, 1H, NH), 9.69 (s, 1H, OH), 12.92 (s, 1H, OH), 12.97 (s, 1H, NH).

Example 24.

6-{4-[*N'*-(2,4-Dihydroxybenzylidene)hydrazino]phenyl}-2,5-dimethyl-2*H*-pyridazin-3-one

Yield: 82 %, mp 266-269 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.16 (d, 3H, CH_3), 3.66 (s, 3H, CH_3), 6.32 (d, 1H, CH), 6.34 (d of d, 1H, CH), 6.84 (d, 1H, CH), 6.97 (d, 2H, CH), 7.32 (d, 1H, CH), 7.36 (d, 2H, CH), 8.10 (s, 1H, CH), 9.69 (s, 1H), 10.36 (s, 1H), 10.61 (s, 1H).

Example 25.

6-{4-[*N'*-(2,4-Dihydroxybenzylidene)hydrazino]phenyl}-2-methyl-2*H*-pyridazin-3-one

Yield: 82.4 %, mp 304-306 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.72 (s, 3H, CH_3), 6.36 (m, 2H, CH), 6.99 (m, 3H, CH), 7.36 (d, 1H, CH), 7.76 (d, 2H, CH), 7.96 (d, 1H, CH), 8.12 (s, 1H, CH), 9.72 (s, 1H), 10.44 (s, 1H), 10.57 (s, 1H).

Example 26.

6-{4-{*N′*-[1-(2,4-dihydroxyphenyl)ethylidene]hydrazino}phenyl}-2-methyl-2*H*-pyridazin-3-one

A solution of 6-(4-hydrazinophenyl)-2-methyl-2*H*-pyridazin-3-one (0.78 g) and 2,4-dihydroxy-acetophenone (0.55 g) in acetonitrile (20.0 ml) was heated under reflux for 5 hrs. Chrystals formed at room temperature were filtered away. On cooling the filtrate overnight the product chrystallized out. This was filtered, washed with warm ethanol and dried under reduced pressure. Yield: 5.6 %, mp 263-268 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 2.35 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 6.30 (s, 1H, CH), 6.34 (d, 1H, CH), 6.99 (d, 1H, CH), 7.09 (d, 2H, CH), 7.39 (d, 1H, CH), 7.82 (d, 2H, CH), 7.99 (d, 1H, CH), 9.58 (s, 1H, NH), 9.71 (s, 1H, OH), 12.90 (s, 1H, OH).

Example 27.

6-{4-{*N′*-[1-(2,4-Dihydroxyphenyl)propylidene]hydrazino}phenyl}-2-methyl-2*H*-pyridazin-3-one

The title compound was prepared according to the general method 2.
Yield: 29 %, mp 225-233 °C.
^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.15 (t, 3H, CH_3), 2.87 (q, 2H, CH_2), 3.73 (s, 3H, CH_3), 6.33 (d, 1H, CH), 6.37 (d of d, 1H, CH), 6.99 (d, 1H, CH) 7.13 (d, 2H, CH), 7.37 (d, 1H, CH), 7.82 (d, 1H, CH), 7.99 (d, 1H, CH), 9.67 (s, 1H), 9.73 (s, 1H), 12.98 (s, 1H).

Example 28.

6-{4-[*N′*-(2,4-Dihydroxy-3-ethylbenzylidene)hydrazino]phenyl}-2-methyl-2*H*-pyridazin-3-one

Yield: 37 %, mp 262-266 °C.
^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.08 (t, 3H, CH_3), 2.61 (q, 2H, CH_2), 3.71 (s, 3H, CH_3), 6.43 (d, 1H, CH), 6.96 (d, 2H, CH), 6.99 (d, 1H, CH), 7.01 (d, 1H, CH), 7.79 (d, 2H, CH), 7.96 (d, 1H, CH), 8.05 (s, 1H, CH), 9.67 (s, 1H), 10.49 (s, 1H), 11.30 (s, 1H).

Example 29.

4-(2,4-Dihydroxyphenyl)-4-{[4-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl]hydrazono}butyric acid

The title compound was prepared according to the general method 2.
Yield:15.9 %, mp 138-141 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.51 (t, 2H, CH_2), 3.06 (t, 2H, CH_2), 3.72 (s, 3H, CH_3), 6.30 (s, 1H, CH), 6.34 (d, 1H, CH), 7.01 (d, 1H, CH), 7.10 (d, 2H, CH), 7.32 (d, 1H, CH), 7.83 (d, 2H, CH), 7.01 (d, 1H, CH), 9.72 (s, 1H), 9.78 (s, 1H), 12.31 (s, 1H), 12.74 (s, 1H).

Example 30 (intermediate).

6-(4-hydrazinophenyl)-5-methyl-2*H*-pyridazin-3-one

The title compound was prepared from 6-(4-aminophenyl)-5-methyl-2*H*-pyridazin-3-one similarly as 6-(4-hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 4.11 (s, 2H, NH_2), 6.75 (s, 1H, CH), 6.81 (d, 2H, CH), 6.95 (s, 1H, NH), 7.21 (d, 2H, CH), 12.82 (s, 1H, NH).

Example 31 (intermediate).

6-(4-hydrazinophenyl)-2,5-dimethyl-2*H*-pyridazin-3-one

The title compound was prepared from 6-(4-aminophenyl)-2,5-dimethyl-2*H*-pyridazin-3-one similarly as 6-(4-hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.14 (d, 3H, CH_3), 3.63 (s, 3H, CH_3), 4.12 (s, 2H, NH_2), 6.81 (d, 2H, CH), 6.82 (d, 1H, CH), 6.98 (s, 1H, NH), 7.22 (d, 2H, CH).

Example 32 (intermediate).

6-(4-hydrazinophenyl)-2-methyl-2*H*-pyridazin-3-one

The title compound was prepared from 6-(4-aminophenyl)-2-methyl-2*H*-pyridazin-3-one similarly as 6-(4-hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.69 (s, 3H, CH_3), 4.18 (s, 2H, NH_2), 6.83 (d, 2H, CH), 6.94 (d, 1H, CH), 7.11 (s, 1H, NH), 7.65 (d, 2H, CH), 7.93 (d, 1H, CH).

Example 33.

6-(4-{N'-[1-(2,4-Dihydroxy-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

The title compound was prepared according to the general method 2.
Yield 74 %, Melting point: 259 –261 °C
^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.21 (d, 1H), 2.35(s, 3H), 2.63-2.68 (m, 1H), 3.30-3.36 (m, 1H), 6.28 (d, 1H), 6.34 (q, 1H), 7.03 (d, 2H), 7.37 (d, 1H), 7.71 (d, 2H), 9.57 (s, 1H), 9.70 (s, 1H), 10.78 (s, 1H), 12.91 (s 1H).

Example 34.

6-(4-{N'-[Bis-(2,4-dihydroxy-phenyl)-methylene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

The title compound was prepared according to the general method 2.
Yield 13 %, Melting point: 150->175 °C
^{1}H NMR (DMSO-d_6): δ = 1.06 (d, 3H), 2.19 (d, 1H), 2.61-2.67 (m, 1H), 3.30-3.36 (m, 1H), 6.16 - 6.19 (q, 1H), 6.03 (d, 1H), 6.37 - 6.39 (q, 1H), 6.47 (d, 1H), 6.55 (d, 1H), 6.84 (d, 1H), 7.02 (d, 2H), 7.66 (d, 2H), 8.93 (broad, 1H), 9.72 (broad, 3H), 10.76 (s, 1H), 12.71 (s 1H).

Example 35.

6-(4-{N'-[1-(2,5-Dihydroxy-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

The title compound was prepared according to the general method 2.
Yield 73 %, Melting point: 279 –284 °C
^{1}H NMR (DMSO-d_6): δ = 1.08 (d, 3H), 2.21 (d, 1H), 2.34 (s, 3H), 2.63-2.69 (m, 1H), 3.32-3.38 (m, 1H), 6.66-6.73 (m, 2H), 6.93 (s, 1H), 7.09 (d, 2H), 7.73 (d, 2H), 8.85 (s, 1H), 9.73 (s, 1H), 10.80 (s, 1H), 11.85 (s, 1H).

Example 36.

6-{4-[N'-(2,4-Dihydroxy-benzylidene)-hydrazino]-phenyl}-5-ethyl-4,5-dihydro-2H-pyridazin-3-one

Yield 29 %, Melting point: 270 –275 °C
^{1}H NMR (DMSO-d_6): δ = 0.87 (t, 3H), 1.38-1.54 (m, 2H), 2.36 (d, 1H), 2.56-2.62 (q, 1H), 3.12-3.38 (m, 1H), 6.32 (m, 2H), 6.93 (d, 2H), 7.33 (d, 1H), 7.67 (d, 2H), 8,08 (s, 1H), 9.68 (s, 1H), 10.34 (s, 1H), 10.55 (s 1H), 10.71 (s, 1H).

Example 37.

N-[4-(1-{[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazono}-ethyl)-phenyl]-acetamide

The title compound was prepared according to the general method 2.

Yield 41 %, Melting point: 145-155 °C

^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.05 (s, 3H), 2.23 (d, 1H), 2.24 (s, 3H), 2.61-2.68 (m, 1H), 3.30-3.36 (m, 1H), 7.24 (d, 2H), 7.60 (d, 2H), 7.67 (d, 2H), 7.74 (d, 2H), 9.45 (s, 1H), 10.01 (s, 1H), 10.75 (s, 1H).

Example 38.

6-(4-{N'-[1-(2,4-Dihydroxy-3-methyl-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield 47 %, Melting point: 244 –248 °C

^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.03 (s, 3H), 2.20 (d, 1H), 2.63-2.68 (m, 1H), 3.30-3.36 (m, 1H), 6.43 (d, 1H), 6.91 (d, 2H), 7.01 (d, 1H), 7.70 (d, 2H), 8.05 (s, 1H), 9.69 (s, 1H), 10.46 (s, 1H), 10.76 (s, 1H), 11.31 (s, 1H)

Example 39.

6-{4-[N'-(3-Acetyl-2,4-dihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield 72 %, Melting point: 268 –270 °C

^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.20 (d, 1H), 2.61-2.66 (m, 1H), 2.69 (s, 3H), 3.30-3.36 (m, 1H), 6.53 (d, 1H), 6.98 (d, 2H), 7.70 (m, 3H), 8.15 (s, 1H), 10.56 (s, 1H), 10.76 (s, 1H), 11.89 (s, 1H), 13.91 (s, 1H)

Example 40.

6-{4-[N'-(3-Ethyl-2,4-dihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield 36 %, Melting point: 238 –240 °C

^{1}H NMR (DMSO-d_6): δ = 1.05-1.09 (m, 3H, 3H), 2.21 (d, 1H), 2.60-2.64 (m, 3H), 3.30-3.36 (m, 1H), 6.42 (d, 1H), 6.90 (d, 2H), 7.00 (d, 1H), 7.71 (d, 2H), 8.04 (s, 1H), 9.65 (s, 1H), 10.46 (s, 1H), 10.76 (s, 1H), 11.31 (s, 1H).

Example 41.

N-(3-Hydroxy-4-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-phenyl)-acetamide

Yield 39 %, Melting point: 269 –275 °C

^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.03 (s, 3H), 2.20 (d, 1H), 2.61-2.67 (m, 1H), 3.28-3.34 (m, 1H), 6.97-7.01 (m, 3H), 7.36 (d, 1H), 7.49 (d, 1H), 7.68 (d, 2H), 8.12 (s, 1H), 9.96 (s, 1H), 10.42 (s, 1H), 10.52 (s, 1H), 10.75 (s, 1H).

Example 42.

6-{4-[N'-(2,4-Dichloro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield 53 %, Melting point: 252 –254 °C

^{1}H NMR (DMSO-d_6): δ = 1.07 (d, 3H), 2.21 (d, 1H), 2.63-2.68 (m, 1H), 3.28-3.37 (m, 1H), 7.13 (d, 2H), 7.45 (q, 1H), 7.64 (d, 1H), 7.70 (d, 2H), 8.04 (d, 1H), 8.19 (s, 1H), 10.78 (s, 1H), 11.02 (s, 1H)

Example 43.

6-{4-[N'-(2,4-Dihydroxy-3-propyl-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield 61 %, Melting point: 160 –170 °C

^{1}H NMR (DMSO-d_6): δ = 0.92 (t, 3H), 1.07 (d, 3H),1.48-1.53 (m,2H), 2.21 (d, 1H), 2.55-2.58 (m, 2H), 2.62-2.68 (m, 1H), 3.30-3.35 (m, 1H), 6.42 (d, 1H), 6.91 (d, 2H), 7.00 (d, 1H), 7.70 (d, 2H), 8.04 (s, 1H), 9.25 (s, 1H), 10.45 (s, 1H), 10.76 (s, 1H), 11.29 (s, 1H)

Example 44.

6-{4-[N'-(3-Butyl-2,4-dihydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield 74 %, Melting point: 218 °C

^{1}H NMR (DMSO-d_6): δ = 0.91 (t, 3H), 1.07 (d, 3H), 1.29-1.38 (m, 2H), 1.45-1.51 (m, 2H), 2.21 (d, 1H), 2.57-2.68 (m, 2H, 1H), 3.29-3.36 (m, 1H), 6.42 (d, 1H), 6.91 (d, 2H), 6.99 (d, 1H), 7.71 (d, 2H), 8.04 (s, 1H), 9.62 (s, 1H), 10.46 (s, 1H), 10.76 (s, 1H), 11.28 (s, 1H).

Example 45 (intermediate).
6-(3-Hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

The title compound was prepared using method of example 1 starting from 1.5 g of 6-(3-aminophenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one (J. Med. Chem. 1974 17(3)). The product was isolated (after addition of sodium hydroxide solution) by extraction to tetrahydrofuran. Crystallisation from acetonitrile yielded 1.0 g of the title compound.
1-HNMR (DMSO-d6, 400 MHz): 1.06 (d, 3H), 2.22 (d, 1H), 2.66 (dd, 1H), 3.30 (m, 1H), 3.97 (s, 2H), 6.78 (s, 1H), 6.81 (m, 1H), 6.98 (m, 1H), 7.14 (t, 1H), 7.23 (t, 1H), 10.86 (s, 1H).

Example 46.
6-(3-{*N*-[Bis(2,4-dihydroxy-phenyl)methylene]hydrazino}phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

A mixture of 6-(3-Hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (0.38 g), 2,2',4,4'-tetrahydroxybenzophenone (0.51 g), acetic acid (0.4 ml), and acetonitrile (7.0 ml) was refluxed for 20 h. Solvents were removed *in vacuo* and the product was separated using column chromatography (silicagel; toluene, ethyl acetate, acetic acid 8:3:3). Crystallisation from a mixture of ethyl acetate and dichloromethane gave 290 mg of product, mp 195-205 °C.

1-HNMR (DMSO-d6, 400 MHz): 1.08 (d, 3H), 2.23 (d, 1H), 2.68 (dd, 1H), 3.31 (m, 1H), 6.17 (dd, 1H), 6,30 (d, 1H), 6.36 (dd, 1H), 6.46 (d 1H), 6,57 (d, 1H), 6.83 (d, 1H), 7.01 (m, 1H), 7.19 (m,1H), 7,28 (t, 1H), 7,45 (t, 1H), 10,92 (s, 1H), 8-14 (broad singlets, 5H).

Example 47.
6-{4-[*N*–(2,4-Dihydroxy-5-nitrobenzylidene)hydrazino]phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

6-(4-Hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (1.10 g), 2,4-dihydroxy-5-nitrobenzaldehyde (0.92 g) and acetic acid (20 ml) were combined and the resulting mixture was refluxed for 20 min. The mixture was cooled to room temperature and the product filtered, yield 1.95 g, solvated crystals with 1 mol of acetic acid, mp about 290 °C with decomposition.

1-HNMR (DMSO-d6, 400 MHz): 1.08 (d, 3H), 1.91(s, 3H), 2.22 (d. 1H), 2.66 (dd, 1H), 3.36 (m, 1H), 6.58 (s, 1H), 7.03 (d, 2H), 7.70 (d, 2H), 8.11 (s. 1H), 8.34 (s, 1H), 10.69 (s, 1H), 10.76 (s, 1H), 13.04 (s, 1H), 13.58 (s, 1H), 13.95 (s, 1H).

Example 48

6-{4-{*N*-[4-(Dimethylamino)benzylidene]hydrazino}phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

6-(4-Hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (1.1 g), 4-(dimethylamino)benzaldehyde (0.83 g), acetic acid (0,60 ml) and acetonitrile (15 ml) were combined and the resulting mixture was heated to boil, cooled to room temperature and the product was filtered and washed with acetonitrile, yield 1.50g, mp 225-232 °C.
1-HNMR (DMSO-d6, 400 MHz): 1.07 (d, 3H), 2.21 (d, 1H), 2.64 (dd, 1H), 2.94 (s, 6H), 3.34 (m, 1H), 6.73 (d, 2H), 7.04 (d, 2H), 7.49 (d, 2H), 7.65 (d, 2H), 7.81 (s, 1H), 10.24 (s, 1H), 10.73 (s, 1H).

Example 49.

6-(4-{*N*-[1-(2,4-Dihydroxy-3-methylphenyl)ethylidene]hydrazino}phenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

The title compound was prepared according to the general method 2.
Yield 41 %, m.p. 268-271 °C.
1-HNMR (DMSO-d6, 400 MHz): 1.07 (d, 3H), 2.20 (d, 1H), 2.65 (dd, 1H), 3.35 (m, 1H), 6.40 (d, 1H), 7.05 (d, 2H), 7.24 (d, 1H), 7.73 (d, 2H), 9.55 (s, 1H), 9.57 (s, 1H), 10.77 (s, 1H), 13.25 (s, 1H).

Example 50.

6-{4-[*N*–(2,4-Dimethoxybenzylidene)hydrazino]phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield 90 %, m.p. 215-218 °C.
1-HNMR (DMSO-d6, 400 MHz): 1.07 (d, 3H), 2.17 (d, 1H), 2.63 (dd, 1H), 3.31 (m, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 6.58-6.61 (m, 2H), 7.03 (d, 2H), 7.65 (d, 2H), 7.78 (d, 1H), 8.16 (s, 1H), 10.43 (s, 1H), 10.73 (s, 1H).

Example 51.

6-{4-[*N*–(2 -Hydroxy-4-methoxybenzylidene)hydrazino]phenyl}-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one

Yield 93 %, m.p. 214-216 °C.

1-HNMR (DMSO-d6, 400 MHz): 1.07 (d, 3H), 2.20 (d, 1H), 2.64 (dd, 1H), 3.34 (m, 1H), 3.75 (s, 3H), 6.46-6.51 (m, 2H), 6.96 (d, 2H), 7.47 (d, 1H), 7.68 (d, 2H), 8.12 (s, 1H), 10.48 (s, 1H), 10.66 (s, 1H), 10.75 (s, 1H).

Example 52.

6-{4-[N'-(4-nitrobenzylidene)-hydrazino]-phenyl}- 5-methyl -4,5-dihydro-2H-pyridazin-3-one

Yield: 80 %, mp 216-217°C

1H NMR (400 MHz, DMSO-d6): δ = 1.08(d,3H), 2.21(d,1H), 2.63-2.66(m,1H), 3.29-3.31(m,1H), 7.19(d,2H), 7.72(d,2H), 7.72 (d,2H), 7.92(s,1H), 7.99(s,1H), 8.24(d,2H),10.80(s,1H), 10.10(s,1H)

Example 53.

6-{4-[N'-(2-Methoxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 78 %, mp 180 -183°C

1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.20(d,1H), 2.62-2.67(m,1H), 3.32-3.34(m,1H), 3.85(s,3H), 6.97-7.00(m,1H), 7.06(d,2H), 7.29-7.32(m, 1H), 7.66 (d,2H), 7.87(d,1H), 8.25(s,1H), 10.61(s,1H), 10.75(s,1H)

Example 54.

6-{4-[N'-(2-Hydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 90 %, mp 265 - 268°C

1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.20(d,1H), 2.62-2.68(m,1H), 3.32-3.36(m,1H), 6.86-6.90(m,1H), 7.01(d,2H), 7.16-7.20(m, 1H), 7.60 (d,2H), 7.69(d,1H), 8.20(s,1H), 10.37(s,1H), 10.64(s,1H), 10.76(s,1H)

Example 55.

6-{4-[N'-(4-Methoxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 82 %, mp 172 - 174°C

1H NMR (400 MHz, DMSO-d6): δ = 1.08(d,3H), 2.19(d,1H), 2.61-2.67(m,1H), 3.29-3.31(m,1H), 3.79(s,3H), 6.98(d,2H), 7.07(d,2H), 7.61 (d,2H), 7.66(s,2H), 7.87(s,1H), 10.43(s,1H), 10.75(s,1H)

Example 56.

2,6-Dihydroxy-3-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-benzoic acid

Yield: 51 %, mp 215 -218°C

1H NMR (400 MHz, DMSO-d6): δ = 1.06(d,3H), 2.20(d,1H), 2.61-2.67(m,1H), 3.30-3.36(m,1H), 6.24(d,1H), 6.99(d,2H), 7.63(d,2H), 7.65(d,1H), 8.16(s,1H), 10.00(s,1H), 10.71(s,1H), 10.90(s,1H)

Example 57.

6-{4-[N'-(2-Hydroxy-3-methoxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 93 %, mp 210 -213°C

1H NMR (400 MHz, DMSO-d6): δ = 1.08(d,3H), 2.20(d,1H), 2.62-2.67(m,1H), 3.35-3.39(m,1H), 3.81(s,1H) 6.82(t,1H), 6.93(d,1H), 7.02(d,2H), 7.22(d,1H), 7.69(d,2H), 8.21(s,1H), 9.88(s,1H), 10.64(s,1H), 10.77(s,1H)

Example 58.

6-{4-[N'-(2-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 77 %, mp 250 -253°C

1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.20(d,1H), 2.63-2.70(m,1H), 3.29-3.36(m,1H), 7.14(d,2H), 7.50-7.54(m,1H), 7.70(d, 2H), 7.71-7.75(m,1H), 7.99(d,1H), 8.17(s,1H), 8.30(s,1H), 10.79(s,1H), 11.11(s,1H)

Example 59.

6-{4-[N'-(2,6-Dinitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 20 %, mp 216-218°C

1H NMR (400 MHz, DMSO-d6): δ = 1.06(d,3H), 2.20(d,1H), 2.63-2.70(m,1H), 3.29-3.36(m,1H), 6.96(d,2H), 7.68-7.74(m,3H), 8.11(s,1H), 8.22(d,2H), 10.81(s,1H), 11.29(s,1H)

Example 60.

4-{[4-(4-Methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazonomethyl}-benzonitrile

Yield: 85 %, mp 246 -248°C
1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.21(d,1H), 2.63-2.67(m,1H), 3.30-3.35(m,1H), 7.16(d,2H), 7.70(d,2H), 7.82 (d,2H), 7.84(d,2H), 7.93(d,2H), 10.79(s,1H), 10.97(s,1H)

Example 61.

6-{4-[N'-(4-Hydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 86 %, mp 258-261°C
1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.19(d,1H), 2.61-2.67(m,1H), 3.30-3.35(m,1H), 6.79(d,2H), 7.04(d,2H), 7.48 (d,2H), 7.65(d,2H), 7.82(s,1H), 9.66(s,1H), 10.33(s,1H), 10.73(s,1H)

Example 62.

6-{4-[N'-(3-Hydroxy-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 80 %, mp 267 -270°C
1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.20(d,1H), 2.61-2.67(m,1H), 3.33-3.36(m,1H), 6.71-6.73(dd,1H), 7.04-7.12(m,4H), 7.18-7.21(m,1H), 7.68(d,2H), 7.82(s,1H), 9.46(s,1H), 10.54(s,1H), 10.76(s,1H)

Example 63.

6-{4-[N'-(4-Hydroxy-3-nitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 21 %, mp 230 - 233°C
1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.19(d,1H), 2.62-2.69(m,1H), 3.31-3.36(m,1H), 7.09(d,2H), 7.16(d,1H), 7.67(d,2H), 7.88(s,1H), 7.89-7.91(dd,1H), 8.11(d,1H), 10.64(s,1H), 10.76(s,1H), 11.00(s,1H)

Example 64.

4-(2,4-Dihydroxy-phenyl)-4-{[4-(4-methyl-6-oxo-1,4,5.6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazono}-butyric acid

Yield: 26 %, mp 299 -302°C
1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.19(d,1H), 2.49-2.51(t,2H), 2.64-2.67(m,1H), 3.03-3.05(t,2H), 3.28-3.31(m,1H), 6.29(d,1H), 6.33-6.35(dd,1H), 7.04(d,2H), 7.32(d,1H), 7.72(d,2H), 9.71(s,1H), 9.79(s,1H), 10.78(s,1H), 12.00(s,1H), 12.77(s,1H)

Example 65.
6-{4-[N'-(2,4-Dinitro-benzylidene)-hydrazino]-phenyl}-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 50 %, mp 278 -280°C
1H NMR (400 MHz, DMSO-d6): δ = 1.07(d,3H), 2.21(d,1H), 2.64-2.70(m,1H), 3.37-3.40(m,1H), 7.22(d,2H), 7.75(d,2H), 8.37(s,1H), 8.43(d,1H). 8.44(d,1H), 8.74(d,1H), 10.84(s,1H), 11.62(s,1H)

Example 66.
5-(2,4-Dihydroxy-phenyl)-5-{[4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-phenyl]-hydrazono}-pentanoic acid

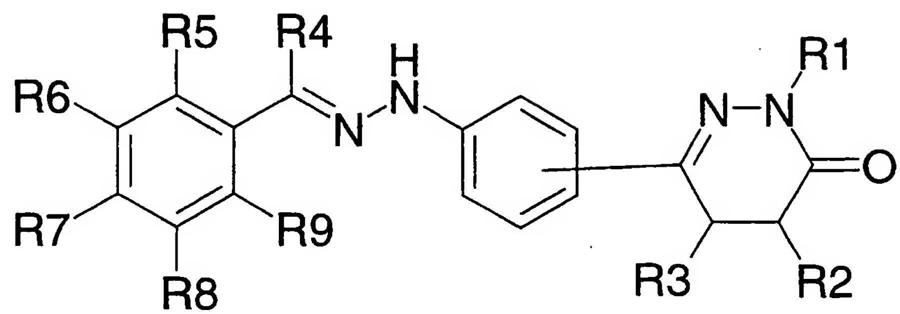
Yield: 39 %, mp 235 - 240°C
1H NMR (400 MHz, DMSO-d6): δ = 1.04-1.08(m,5H), 1.72-1.74(m,2H), 2.22(d,1H), 2.64-2.67(m,1H), 2.80-2.82(m,2H), 3.30-3.36(m,1H), 6.29(d,1H), 6.32-6.35(dd,1H), 7.04(d,2H), 7.41(d,1H), 7.72(d,2H), 9.77(s,1H), 9.71(s,1H), 10.78(s,1H), 12.00(s,1H), 12.88(s,1H)

Example 67.
6-(4-{N'-[1-(4-Hydroxy-3-methoxy-2-nitro-phenyl)-ethylidene]-hydrazino}-phenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Yield: 46 %, mp 251 -254°C
1H NMR (400 MHz, DMSO-d6): δ = 1.06(d,3H), 2.19(d,1H), 2.21(s,3H), 2.61-2.65(m,1H), 3.30-3.36(m,1H), 3.83(s,3H), 7.06(d,2H), 7.08(d,2H), 7.28(d,2H), 7.63(d,1H), 9.49(s,1H), 10.55(s,1H), 10.75(s,1H)

Claims

Compounds of formula (I):



(I)

in which

R_1 to R_4 means hydrogen, alkyl, alkenyl, aryl, arylalkyl, carboxyalkyl, hydroxyalkyl or halogenalkyl, or R_2 and R_3 form a ring of 5-7 carbon atoms,

R_5 to R_9 means hydrogen, alkyl, alkenyl, aryl, arylalkyl, acyl, hydroxy, alkoxy, alkoxycarbonyl, amino, acylamino, alkylamino, aryloxy, halogen, cyano, nitro, carboxy, alkylsulfonyl, sulfonamido or trifluoromethyl,

wherein each aryl residue defined above by itself or as a part of another group may be substituted,

and pharmaceutically acceptable salts and esters thereof,

provided that a) when R_1, R_2, R_3, R_5, R_6, R_8 and R_9 are hydrogen and R_4 is methyl, R_7 is not hydrogen or methoxy and b) when R_1, R_2, R_3, R_5, R_6, R_7 and R_8 are hydrogen and R_4 is methyl, R_9 is not hydroxy.

2. Compound of claim 1 wherein R_5 to R_9 are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{6-10} aryl, C_{7-12} arylalkyl, C_{1-6} acyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, amino, C_{1-6} acylamino, C_{1-6} alkylamino, C_{6-10} aryloxy, halogen, cyano, nitro, carboxy, C_{1-6} alkylsulfonyl, sulfonamido or trifluoromethyl.

3. Compound of claim 2 wherein R_5 to R_9 are independently hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, carboxy, C_{1-6} alkoxycarbonyl or nitro.

4. Compound of claim 3 wherein R_5 is hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, carboxy, C_{1-6} alkoxycarbonyl or nitro.

5. Compound of claim 4 wherein R_5 is hydroxy or nitro.

6. Compound of any of claims 1-5 wherein R_1 to R_4 are independently hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{6-10} aryl, C_{7-12} arylalkyl, C_{1-6} carboxyalkyl, C_{1-6} hydroxyalkyl or C_{1-6} halogenalkyl, or R_2 and R_3 form a phenyl ring.

7. Compound of any of claims 1-6 wherein R_1 to R_3 are independently hydrogen or C_{1-6} alkyl.

8. Compounds of formula (I) in which R_1, R_2, R_3, R_5, R_6, R_8 and R_9 are hydrogen, R_4 is methyl, and R_7 is hydrogen or methoxy, or in which R_1, R_2, R_3, R_5, R_6, R_7 and R_8 are hydrogen, R_4 is methyl and R_9 is hydroxy and pharmaceutically acceptable salts and esters thereof, for use as a medicament.

9. Pharmaceutical composition comprising a compound of claim 1 as an active ingredient together with a pharmaceutically acceptable carrier.

10. Method for the treatment of congestive heart failure comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI 01/00241

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D237/04 C07D237/32 A61K31/50 A61P9/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBASE, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 223 937 A (BOEHRINGER MANNHEIM GMBH) 3 June 1987 (1987-06-03) page 15 -page 18; examples 4,6,7,13-17	1-7
X	MERTENS A ET AL: "Nonsteroidal Cardiotonics. 3. New 4,5-Dihydro-6-(1H-indol-5-yl)pyridazin-3(2H)-ones and Related Compounds with Positive Inotropic Activities" JOURNAL MED. CHEM., vol. 33, no. 10, 1990, pages 2870 -2875, XP002901789 starting materials to compounds 6-9, page 2874	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2001	17.07.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Eva Johansson

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI 01/00241

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 383 449 A (ORION YHTYMAE OY) 22 August 1990 (1990-08-22) page 3, line 4 - line 5 page 7, line 37 - line 39 page 11 -page 12; example 16	10
X	GB 2 228 004 A (ORION YHTYMAE OY) 15 August 1990 (1990-08-15) page 16; example 16 abstract	10
X	WO 99 16443 A (ORION CORPORATION) 8 April 1999 (1999-04-08) abstract	10

1

INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/FI 01/00241

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 10

Claim 10 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/ Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FI 01/00241

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0223937	A	03-06-1987	DE	3531658	A	12-03-1987
			AT	73797	T	15-04-1992
			AU	572405	B	05-05-1988
			AU	6216686	A	12-03-1987
			DD	258229	A	13-07-1988
			DE	3684415	A	23-04-1992
			DK	419086	A	06-03-1987
			ES	2001936	A	01-07-1988
			FI	863564	A	06-03-1987
			GR	862248	A	31-12-1986
			HU	41770	A,B	28-05-1987
			IL	79911	A	15-04-1991
			JP	62056486	A	12-03-1987
			NZ	217419	A	29-03-1989
			PT	83310	A,B	01-10-1986
			US	4851406	A	25-07-1989
			ZA	8606705	A	29-04-1987
EP 0383449	A	22-08-1990	AT	127456	T	15-09-1995
			AU	619648	B	30-01-1992
			AU	4929690	A	16-08-1990
			CA	2009678	A,C	11-08-1990
			CN	1044811	A,B	22-08-1990
			CZ	9000557	A	13-10-1999
			DD	293112	A	22-08-1991
			DE	69022078	D	12-10-1995
			DE	69022078	T	22-02-1996
			DK	383449	T	02-01-1996
			ES	2078939	T	01-01-1996
			FI	96511	B	29-03-1996
			GB	2228004	A,B	15-08-1990
			GR	3017510	T	31-12-1995
			HU	53090	A,B	28-09-1990
			HU	59384	A	28-05-1992
			JP	2288868	A	28-11-1990
			JP	3011955	B	21-02-2000
			LT	1233	A,B	25-04-1995
			NO	178067	B	09-10-1995
			NZ	232257	A	26-03-1991
			PT	93111	A,B	31-08-1990
			SK	55790	A	14-02-2000
			RU	2048467	C	20-11-1995
			SU	1836362	A	23-08-1993
			RU	2068844	C	10-11-1996
			US	5019575	A	28-05-1991
			US	5185332	A	09-02-1993
			US	5122524	A	16-06-1992
			ZA	9000681	A	31-10-1990
GB 2228004	A	15-08-1990	AT	127456	T	15-09-1995
			AU	619648	B	30-01-1992
			AU	4929690	A	16-08-1990
			CA	2009678	A,C	11-08-1990
			CN	1044811	A,B	22-08-1990
			CZ	9000557	A	13-10-1999
			DD	293112	A	22-08-1991
			DE	69022078	D	12-10-1995
			DE	69022078	T	22-02-1996

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FI 01/00241

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2228004 A		DK 383449 T	02-01-1996
		EP 0383449 A	22-08-1990
		ES 2078939 T	01-01-1996
		FI 96511 B	29-03-1996
		GR 3017510 T	31-12-1995
		HU 53090 A,B	28-09-1990
		HU 59384 A	28-05-1992
		JP 2288868 A	28-11-1990
		JP 3011955 B	21-02-2000
		LT 1233 A,B	25-04-1995
		NO 178067 B	09-10-1995
		NZ 232257 A	26-03-1991
		PT 93111 A,B	31-08-1990
		SK 55790 A	14-02-2000
		RU 2048467 C	20-11-1995
		SU 1836362 A	23-08-1993
		RU 2068844 C	10-11-1996
		US 5019575 A	28-05-1991
		US 5185332 A	09-02-1993
		US 5122524 A	16-06-1992
		ZA 9000681 A	31-10-1990
WO 9916443 A	08-04-1999	FI 973804 A	27-03-1999
		AU 732489 B	26-04-2001
		AU 9350698 A	23-04-1999
		BG 104250 A	29-12-2000
		BR 9813213 A	29-08-2000
		CN 1271282 T	25-10-2000
		EP 1014987 A	05-07-2000
		HR 20000171 A	31-12-2000
		HU 0003757 A	28-05-2001
		NO 20001585 A	27-03-2000
		PL 339461 A	18-12-2000
		SK 3842000 A	12-09-2000
		TR 200000635 T	21-09-2000

Form PCT/ISA/210 (patent family annex) (July 1992)